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# Body Mass Index and Early CD4+ T-cell Recovery among Adults Initiating Antiretroviral Therapy in North America, 1998–2010

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## Abstract

**Objective—**Adipose tissue affects several aspects of the cellular immune system, but prior epidemiologic studies have differed on whether a higher body mass index (BMI) promotes CD4+ T-cell recovery on antiretroviral therapy (ART). The objective of this analysis was to assess the relationship between BMI at ART initiation and early changes in CD4 T-cell count.

**Methods—**We used the NA-ACCORD dataset to analyze the relationship between pre-treatment BMI and 12 month CD4+ T-cell recovery among adults who started ART between 1998 and 2010 and maintained HIV RNA levels <400 copies/ml for at least 6 months. Multivariable regression models were adjusted for age, race, sex, baseline CD4+ count and HIV RNA level, year of ART initiation, ART regimen, and clinical site.

**Results—**8,381 participants from 13 cohorts contributed data; 85% were male, 52% were non-white, 32% were overweight (BMI 25–29.9 kg/m$^2$), and 15% were obese (BMI >30 kg/m$^2$). Pre-treatment BMI was associated with 12 month CD4+ T-cell change ($p<0.001$), but the relationship was non-linear ($p<0.001$). Compared with a reference of 22 kg/m$^2$, a BMI of 30 kg/m$^2$ was associated with a 36 cells/μl (95% CI: 14, 59) greater CD4+ T-cell count recovery among women and a 19 cells/μl (95% CI: 9, 30) greater recovery among men at 12 months. At a BMI over 30 kg/m$^2$, the observed benefit was attenuated among men to a greater degree than among women, although this difference was not statistically significant.

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**Conclusions—**A BMI of approximately 30 kg/m$^2$ at ART initiation was associated with greater CD4+ T-cell recovery at 12 months compared to higher or lower BMI values, suggesting adipose tissue may affect peripheral CD4+ T cell recovery.

### Keywords

HIV; antiretroviral therapy; immune reconsitition; nutrition; obesity

## Introduction

Recovery of peripheral CD4+ T-cells following the initiation of antiretroviral therapy (ART) for HIV infection is clinically important for long-term health outcomes (1, 2). Immune reconstitution is a highly variable process with host and disease-state determinants. Prior studies have found that factors such as younger age and white race were associated with more robust CD4+ T-cell gains on ART (3, 4). Recent studies have also reported that nutritional status, namely a body mass index (BMI) in the overweight (25.0–29.9 kg/m$^2$) and even obese (≥30.0 kg/m$^2$) range may confer an advantage in this regard, though the findings have not been uniform (5–9).

Clarifying the relationship between BMI and CD4+ T-cell recovery is important for a deeper understanding of the biological determinants of immune reconstitution. Prior studies in this area were generally limited to single cohorts, and not all studies accounted for the effects of incomplete HIV-1 virologic suppression (5–9). In this analysis, we used the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) to assess the effect of pre-treatment BMI and several other clinical characteristics on early immune recovery among patients achieving sustained virologic suppression on ART.

## Methods

NA-ACCORD is a multi-site collaboration involving 25 cohort studies representing over 100 clinical and research sites for HIV-infected persons in the United States and Canada, and one of the regional cohort study groups supported by the International Epidemiologic Databases to Evaluate AIDS consortium (IeDEA) of the National Institutes of Health. Details about NA-ACCORD have been described previously (10). Briefly, NA-ACCORD collects standardized data on demographic characteristics, antiretroviral medications, laboratory values, clinical diagnoses, and vital status on cohort participants; approximately one third of the participating sites also report longitudinal BMI values on all subjects. Data are transmitted to a centralized core at regular intervals for quality control and harmonization. Institutional review boards at each participating site have reviewed and approved the activities of NA-ACCORD.

We assessed the relationship between BMI at the time of ART initiation and CD4+ T-cell recovery over the first year of treatment among ART-naïve adults starting a first treatment regimen (defined as three or more antiretroviral agents) from 1998 to 2010 in a subset of NA-ACCORD cohorts reporting BMI data. The outcome of interest was change in absolute CD4+ T-cell count from pre-treatment (baseline) to 12 months of continuous ART use. Because the effects of ART on BMI and CD4+ T cell count can begin shortly after starting

treatment, pre-treatment BMI was defined as the closest measurement within 180 days before to 30 days after ART initiation. Similarly, baseline CD4+ T-cell count was defined as the closest laboratory value within 180 days before to 30 days after initiating ART. The 12 month CD4+ T-cell count value was the closest measurement 180 days before or after that time point. We excluded any patients who were recorded as deceased or lost-to-follow up prior to 12 months of treatment.

To reduce the confounding effects of ART adherence and effectiveness, we limited the analysis to participants achieving and maintaining virologic suppression (i.e., a plasma HIV-1 RNA level below 400 copies/ml) for greater than 50% of the 12 month follow-up period (i.e., more than 6 months of the first year of ART). This was calculated by adding the cumulative number of days following each plasma HIV-1 RNA measurement below 400 copies/ml within the first 365 days of ART. While participants recorded as deceased or lost to follow-up prior to 12 months of ART were excluded, the method for calculating virologic suppression assumed the remaining participants were actually alive and in care during the first 365 days. The criteria for whether a participant had evidence of virologic suppression for more than 6 months were entirely independent from the timing of 12 month CD4 count. The determination that a participant maintained virologic suppression for more than 50% of the first 12 months of ART was a dichotomous classification based solely on HIV-1 RNA data from the first 365 days of treatment, while the timing of the 12 month CD4 count was based on the closest value within 180 days on either side of 12 months, and was not in any way affected by the timing of the viral load measurements. The median number of recorded HIV-1 RNA values in the first year among all participants was 4 (interquartile range: 3–5). Because pregnancy status is not recorded in the NA-ACCORD database and unrecorded pregnancies could have potential confounding effects on immune cell subsets, we also excluded female patients with more than a 10% change in weight over the 12 month observation period (n=1134).

Multivariable linear regression was used to assess the relationship between the baseline variables, including BMI, and CD4+ T-cell recovery at 12 months. Individual level variables in the model included BMI, age, sex, race (white versus nonwhite), baseline CD4+ T-cell count and plasma HIV-1 RNA ($\log_{10}$ transformed), initial ART regimen (protease inhibitor [PI]-based, non-nucleoside reverse transcriptase inhibitor [NNRTI]-based, nucleoside reverse transcriptase inhibitors [NRTI] only, or other), and year of ART initiation. Clinical site was the only cohort-level variable included in the model. BMI was fit using a 4 knot restricted cubic spline and all other continuous variables were fit with 3 knots. As sex might be a potential effect modifier in the relationship between BMI and CD4+ T-cell change, an interaction term between sex and BMI was also included. Because BMI was allowed to be non-linear, comparisons of CD4+ T-cell change at the arbitrary BMI-levels of 18.5, 22, 25, 30, 35, and 40 $kg/m^2$ were reported.

The primary analysis was conducted using complete case data; a secondary analysis imputed values for missing baseline viral load data. A sensitivity analysis included data on history of an AIDS-defining event (ADE) prior to starting treatment, self-reported history of injection drug use, and hepatitis C co-infection in the subset of patients with this information. Because ART treatment could affect both BMI and CD4+ T cell count within the first 30

days of ART, we completed a second sensitivity analysis which narrowed the window for BMI and CD4+ T-cell measurements to 90 days prior to ART initiation, and also narrowed the window for the 12 month CD4+ T-cell count to 90 days on either side of 12 months. P-values were calculated using a modified Wald test. Analyses were performed using R (version 2.12.1; www.r-project.org).

## Results

Data on 14,084 HIV-infected, ART naive individuals who started treatment from 1998 through 2010 and had a baseline BMI value recorded were available from 13 cohorts in NA-ACCORD. Among these, 12,049 participants achieved a plasma HIV-1 RNA level below 400 copies/ml within 12 months of starting treatment. The analysis cohort comprised the 8,381 (70%) participants who had a HIV-1 RNA measurement below 400 copies/ml within the first 6 months of ART and maintained virologic suppression for at least 50% of initial 365 days of treatment, of which 3% were underweight (BMI <18.5 kg/m$^2$), 49% had a normal BMI (18.5–24.9 kg/m$^2$), 32% were overweight (BMI 25.0–29.9 kg/m$^2$), 13% were obese (BMI 30.0–40.0 kg/m$^2$), and 2% were morbidly obese (BMI >40 kg/m$^2$) (Supplementary Table). Patients excluded due to detectable viremia for over 50% of follow-up had a similar median age and BMI, and similar sex distribution, but were more likely to be non-white and had a lower median CD4+ T cell count at ART initiation (195 vs. 252 cells/μL).

The relationship between BMI and 12 month CD4+ T-cell change was statistically significant ($p<0.001$) and nonlinear ($p< 0.001$; see Figure). The Table shows CD4+ T-cell change at the arbitrary BMI-levels of 18.5, 25, 30, 35, and 40 kg/m$^2$ extracted from the linear model and compared to a reference of 22 kg/m$^2$ (i.e., the approximate midpoint of the normal BMI range). However, the measure of overall statistical association is not based on any specific BMI comparison, but rather the entire relationship across all BMI levels. For example, a BMI of 30 kg/m$^2$ was associated with a higher 12-month CD4+ T-cell gain among women (36 cells/μL) and men (19 cells/μL) compared to the reference of 22 kg/m$^2$. Among women the higher CD4+ T-cell gain persisted at the BMI levels of 35 kg/m$^2$ (36 cells/μL) and 40 kg/m$^2$ (31 cells/μL) compared to the reference, while among men the effect was attenuated and the CD4+ T-cell gain was less pronounced at a BMI of 35 kg/m$^2$ (16 cells/μL) and 40 kg/m$^2$ (10 cells/μL), although this difference in BMI by sex was not statistically significant. Of note, underweight women (e.g., BMI 18.5 kg/m$^2$) had CD4+ T-cell gains approximately 60% as high as those with BMI 30 kg/m$^2$, though the confidence interval widened markedly at lower BMI values and similar findings were not observed for men. Overall, men had lower CD4+ recovery compared to women ($p<0.001$), but the interaction of sex and BMI did not appear to be an important determinant ($p=0.42$ for the interaction term).

Baseline CD4+ T-cell count, age, and $\log_{10}$ viral load, and the composition of the first-line ART regimen were also associated with CD4+ recovery in the model ($p\leq0.04$ for all), but race was not. Inferences were similar when the model was further adjusted for history of an ADE, intravenous drug use, or hepatitis C coinfection in the subset with available data, when the window period for baseline BMI and CD4+ count was shorted to 90 days pre-ART

and the 12 month CD4+ count window to 90 days (which reduced the cohort from 8381 to 7572 patients with viral suppression), and when missing pre-treatment viral load was imputed in the 3% of cases without this information (data not shown).

## Discussion

In this analysis of over 8,000 HIV-infected adults starting ART and achieving virologic suppression in the United States and Canada, a BMI of 30 kg/m$^2$ (the value commonly used to separate the categories of overweight and obese) at the time of treatment initiation was associated with greater 12 month CD4+ T-cell recovery compared to higher and lower BMI values. Among women, the beneficial effect of higher BMI was largely preserved over a BMI of 30 kg/m$^2$, while in men the CD4+ T-cell gain attenuated as they became progressively more obese. These results support findings described in prior, smaller studies. However, the far larger number of participants in this analysis, drawn from multiple, geographically separated cohorts in North America and all with sustained virologic suppression for the majority of the observation period, permitted the modeling of continuous variables in a non-linear fashion and provided a more complete description of CD4+ T-cell recovery across the BMI spectrum. The finding that greater adipose tissue is associated with peripheral CD4+ T cell recovery on ART should be explored further in translational studies to understand the mechanisms and potential therapeutic implications.

The health outcomes of overweight and obese HIV-infected individuals are increasingly relevant to clinical care as the BMI distribution of patients starting ART today resembles the BMI distribution of the general population in many areas (11, 12). A recent single-cohort study of HIV-infected adults in the U.S. Southeast (a region with a high prevalence of obesity) found 12 month CD4+ lymphocyte gains after ART initiation were greatest among those with a pre-treatment BMI of 25 to 30 kg/m$^2$, and diminished above and below this range (8). Two similar analyses from the US Military HIV Natural History Study found that being either underweight or obese conferred a significantly lower adjusted gain in CD4+ T-cells post-ART compared to normal weight patients (5, 6). Lastly, an analysis of ART-naïve, HIV-infected men in the ACTG Longitudinal Linked Randomized Trials (ALLRT) cohort found CD4+ T-cell recovery was significantly higher at 144 weeks among overweight (35 cells/μl) and obese (113 cells/μl) patients achieving virologic suppression compared to those with normal BMI (7).

The physiologic basis linking adiposity and peripheral CD4+ T-cell populations in treated HIV is unclear at present. Persons with non-HIV related lipodystrophy have peripheral CD4+ T-cell counts in the low-normal range (13, 14), while poor nutrition is associated with reduced circulating lymphocytes (15) and a reversal of the T-helper/suppressor ratio (16). A longitudinal survey of HIV uninfected women found that being overweight, obese, or morbidly obese was independently associated with higher CD4+ T-cell and total lymphocyte counts compared to being normal weight (17). Lastly, a recent cross-sectional study of normal-weight, overweight, and obese HIV uninfected adults found BMI was positively associated with the total number of Th1-type CD4+ T-cells and a higher Th1/Th2 ratio (18). These findings from HIV-uninfected persons suggest that higher adiposity may promote increased peripheral CD4+ T-cell counts, and recent research has shown adipocyte-derived

adipokines, such as leptin, affect a range of cellular immune processes (19). However, the relatively robust CD4+ T cell recovery of underweight women, a group with low baseline CD4+ counts, suggests that body composition may just be one of many factors in early recovery from more severe immunosuppression.

While our analysis benefitted from a large sample size, there may have been unrecognized confounders (e.g., patient behaviors) related to BMI which could have affected the outcome. BMI is an imprecise measure of actual body composition compared to MRI or dual energy X-ray absorptiometry (DEXA) imaging, and heterogeneity in adipose and lean tissue mass and distribution can be present in two patients with the same BMI value. Furthermore, a shorter time to virologic suppression among heavier patients could confer an advantage in immune recovery, but in the absence of daily or weekly plasma measurements we could not evaluate this possibility. Our determination of virologic suppression, required for inclusion in the analysis, was based on data from the initial 365 days of ART, while the selection of the 12-month CD4+ T-cell count value was based on the closest measurement within a window period. Because the time-frame for determining virologic suppression status was independent of the timing of the CD4+ T-cell determination, there may have been a handful of patients who developed viral rebound after 365 days, but still contributed a CD4+ measurement. Lastly, the finding that age, pre-treatment CD4+ T-cell count, viral load, and the initial ART regimen were also associated with CD4+ T-cell recovery suggests BMI is one element in a complex interplay of factors.

In summary, this analysis of over 8,000 patients from diverse cohorts in both the United States and Canada found a BMI of approximately 30 $kg/m^2$ was associated with more robust early CD4+ T-cell recovery, which appeared to be more pronounced in women. Further studies are needed to understand the biological linkages between adiposity and cellular immune function in the setting of HIV infection, and whether opportunities for therapeutic interventions exist.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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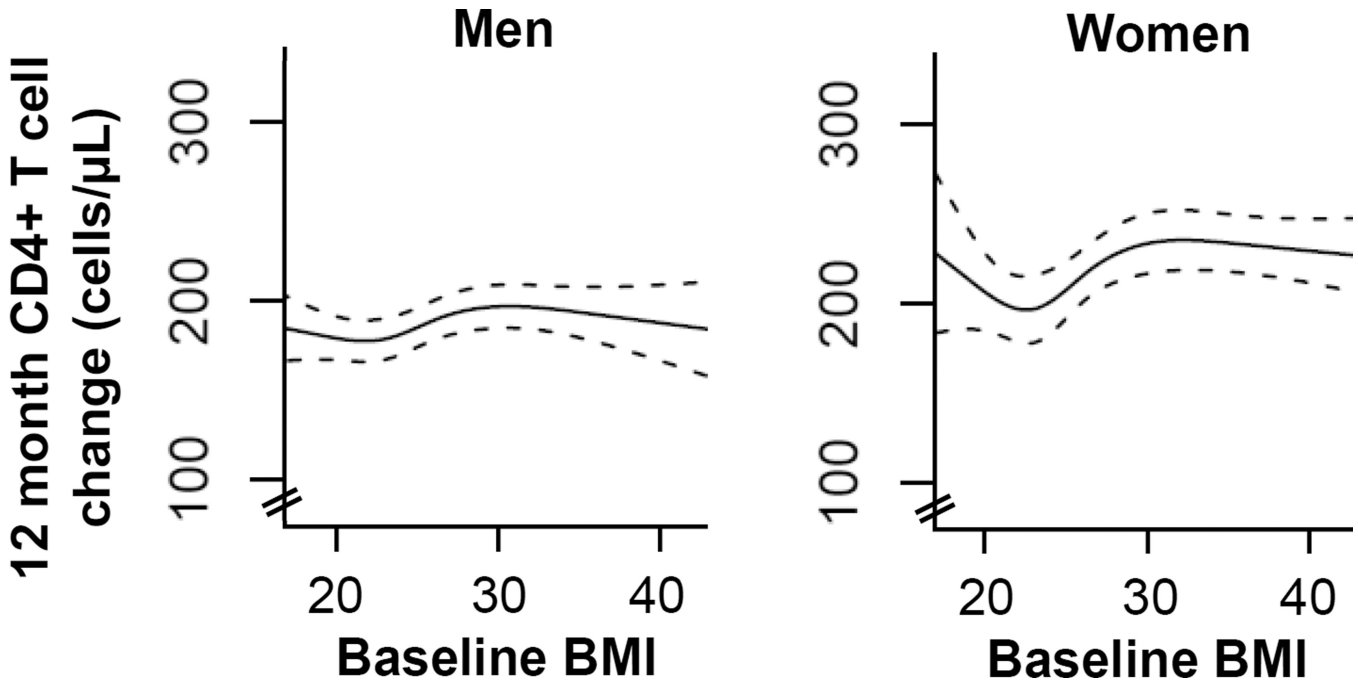


**Figure.**

Relationship of BMI at ART initiation and 12 month CD4+ T-cell recovery among NA-ACCORD participants with virologic suppression

## Table

Multiple regression model of CD4+ lymphocyte count change at 12 months after antiretroviral therapy initiation among NA-ACCORD participants achieving virologic suppression (n=8381)

| Covariate | Effect on CD4 change at 12 months (cells/μL) | 95% confidence interval | P value |
|---|---|---|---|
| Baseline body mass index (kg/m$^2$): | | | |
| Females: | | | <0.001 |
| 18.5 vs. 22 | 21 | (−10, 51) | |
| 25 vs. 22 | 10 | (1, 20) | |
| 30 vs. 22 | 36 | (14, 59) | |
| 35 vs. 22 | 36 | (14, 59) | |
| 40 vs. 22 | 31 | (9, 53) | |
| Males: | | | |
| 18.5 vs. 22 | 4 | (−6, 15) | |
| 25 vs. 22 | 7 | (3, 12) | |
| 30 vs. 22 | 19 | (9, 30) | |
| 35 vs. 22 | 16 | (4, 28) | |
| 40 vs. 22 | 10 | (−9, 30) | |
| Baseline CD4+ count (cells/μl) | | | <0.001 |
| 50 vs. 200 | −23 | (−29, −17) | |
| 100 vs. 200 | −14 | (−18, −10) | |
| 350 vs. 200 | 0 | (−3, 4) | |
| 500 vs. 200 | −20 | (−26, −15) | |
| Baseline age (years) | | | <0.001 |
| 30 vs. 40 | 18 | (12, 24) | |
| 35 vs. 40 | 9 | (7, 11) | |
| 45 vs. 40 | −8 | (−10, −6) | |
| 50 vs. 40 | −16 | (−21, −11) | |
| Baseline $\log_{10}$ HIV-1 RNA | | | <0.001 |
| 4 log vs. 5 log | 44 | (39, 48) | |
| 6 log vs. 5 log | −43 | (−51, −35) | |
| Nonwhite race | −7 | (−14, 1) | 0.18 |
| First antiretroviral therapy regimen (PI-based regimen is the reference group) | | | 0.04 |
| NNRTI-based | −4 | (−11, 3) | |
| NRTI only | −15 | (−32, 1) | |
| Other | 18 | (−2, 37) | |
| Year of ART initiation | | | 0.24 |
| 1998 vs. 2002 | −8 | (−19, 2) | |
| 2000 vs. 2002 | −4 | (−9, 1) | |
| 2004 vs. 2002 | 2 | (−1, 6) | |
| 2006 vs. 2002 | 2 | (−2, 7) | |

| Covariate | Effect on CD4 change at 12 months (cells/μL) | 95% confidence interval | P value |
|---|---|---|---|
| 2008 vs. 2002 | 0 | (−7, 7) | |
| 2010 vs. 2002 | −3 | (−15, 7) | |

BMI was fit using a 4 knot restricted cubic spline and all other continuous variables were fit with 3 knots to avoid assuming linearity.
P-values for non-linear terms: baseline BMI <0.001, baseline CD4+ count <0.001, age 0.55, $\log_{10}$ HIV RNA 0.77, and year of ART initiation 0.11.
Interaction term for BMI and sex p=0.4.
Results were similar when the model was further adjusted for history of an ADE, intravenous drug use, or hepatitis C coinfection (p-value for BMI effect remained <0.001), and when missing baseline viral load data was imputed.

Abbreviations: NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor